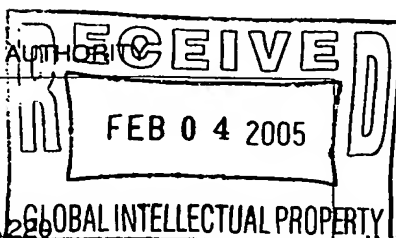


INTERNATIONAL COOPERATION TREATY

HPM / AHF / Julie

From the
INTERNATIONAL SEARCHING AUTHORITY

DOCKETED



PCT

Docket No: PR 60351 W
Attorney: AHF
Paper: Written Opinion
Due Date: 27 MAR 2005
Deadline: 27 MAR 2005
Received: M

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

PR 60351 WD

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/024308

International filing date (day/month/year)
27.07.2004

Priority date (day/month/year)
28.07.2003

International Patent Classification (IPC) or both national classification and IPC
C07C59/72, C07C235/34, C07D207/333, C07D335/02, C07D211/60, C07D309/22, C07C233/25, C07C43/295,

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Goetz, G

Telephone No. +49 89 2399-8105



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**International application No.
PCT/US2004/024308

IAF20REGCIVIL 20 JAN 2006

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/024308

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 27, 36-38

because:

- ☒ the said international application, or the said claims Nos. 36-38 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 27
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2004/024308

Box No. V Reasoned statement under Rule 43*b/s*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	25,26
	No: Claims	1-24,27-38
Inventive step (IS)	Yes: Claims	
	No: Claims	1-38
Industrial applicability (IA)	Yes: Claims	1-35
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/024308

- D1: MUTHYALA ET AL.: "Bridged Bicyclic Cores Containing a 1,1-Diarylene Motif Are High-Affinity Subtype-Selective Ligands for the Estrogen Receptor" J MED CHEM, vol. 46, 4 February 2003 (2003-02-04), pages 1589-1602, XP002313260
- D2: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; GILBERT, JACQUES ET AL.: "Inhibition of prostaglandin synthetase by di- and triphenylethylene derivatives: a structure-activity study" XP002313261 retrieved from STN Database accession no. 98:154902
- D3: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; JENDRALLA, H. ET AL.: "Synthesis and biological activity of new HMG-CoA reductase inhibitors. 3. Lactones of 6-phenoxy-3,5-dihydroxyhexanoic acids" XP002313262 retrieved from STN Database accession no. 115:183017
- D4: US-A-3 287 397 (ALFRED WAHLSTAM HANS ERIK ET AL) 22 November 1966 (1966-11-22)

A. Re Item III.

1. No search has been performed for present claim 27.
Claim 27 does not meet the requirement of Rule 6.2(a).
No examination will done for this claim.
2. For the assessment of the present claims 36 to 38 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims 36 to 38 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

B Re Item V

1. The documents D1 to D4 disclose compounds falling within the subject matter of present claims 1 to 38 (see the citations in the search report).

The present application does therefore not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 24, 28 to 38 is not new in the sense of Article 33(2) PCT.

2. D1 is considered to represent the closest prior art document. It discloses Diarylene-ethylene-derivatives which act as modulators of the estrogen-receptor. In particular D1 discloses a compound (see table 1: compound 9) which falls within the scope of the general formula (I) of present claim 1.

All compounds falling within the scope of general formula (I) of claim 1 are to be considered as all being equivalents and obvious alternatives to each other and as representing a solution to the problem of providing compounds useful as modulators of the estrogen receptor.

Since in the prior art of D1 a compound (compound 9) is disclosed falling within the scope of the general formula (I) of claim 1 and since this compound does solve the underlying problem due to its affinity to the estrogen receptor, all compounds different from compound 9 of D1 but falling under the structure of formula (I) have to be regarded as being obvious alternatives to this known compound.

Consequently no inventive step can be acknowledged for these obvious alternatives in the absence of any surprising effect. Such an effect is not evident from the data presented in present application.

Consequently the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1 to 38 does not involve an inventive step in the sense of Article 33(3) PCT.

C.

1. The definition "solvates" or "pharmacologically functional derivatives" are considered to be not clear in the sense of Article 6 PCT for the definition of a chemically compound: such solvates or derivatives have to be clearly defined by the chemical structure.
2. Lines 15 to 20 of page 175 render the subject matter of present claims unclear.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2004/024308